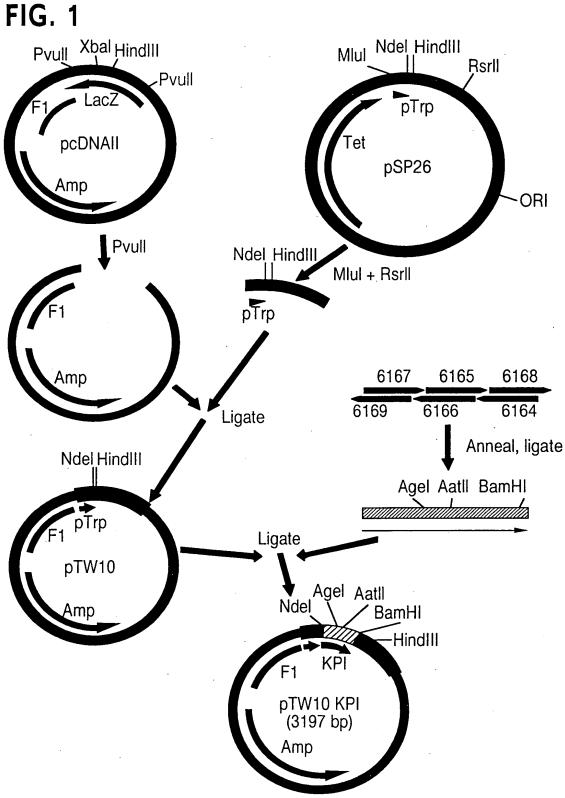


Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604





U U a

AGG

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 10/076,604

.; 7

Val GGA <u>1</u>33 교 Phe Leu AAT Leu 99 AAT Leu GAG Len Ala CG TS GAC Leu TAA TGA 그

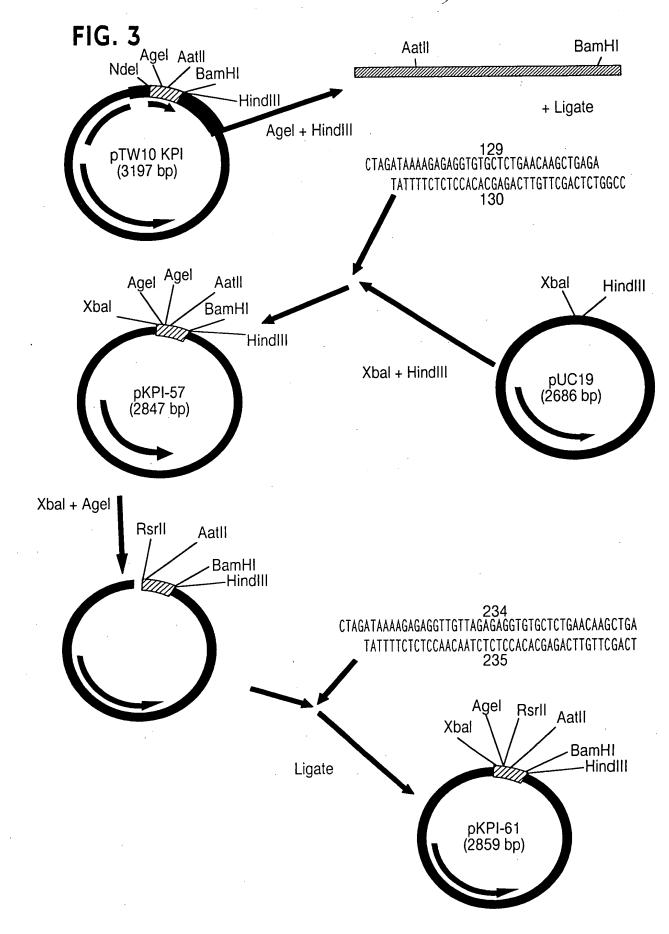
TAC ACG 286 ACC J2C

AAA AAG CGA 글 Sal Sal AAA TAC

TAA CGA GGA CAC Sal Asn AAC



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604





PEPTIDES

Title: PROTEASE INHIBITOR

Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

Rsrl

Agel

255 CCA GAG CIC CGA

AGA

GAG

AAA

GAT

Ser

Val

<u>ප</u> ල

Asp

SGI CGA AAG TGA GAC AAA ACC AGG Ser TAG TAC Met GCA

GAG CTC Glu GAA CIGGAC AAA AAC TTGAAC TILG AAC TTG 999 555 299 TGC ACG ATG AAA AAG

GCT CGA]]C GGA TGC TAC

AGG



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

GAG GAG AGA

AAA

CICAGA ACG CAC

Ser

Val

Val

TGA CIGGAC AAA TCC

360

TGA CTG AAA TTGTTG GCA TTG 900 GGT ATG AAG

GAA CITT Glu

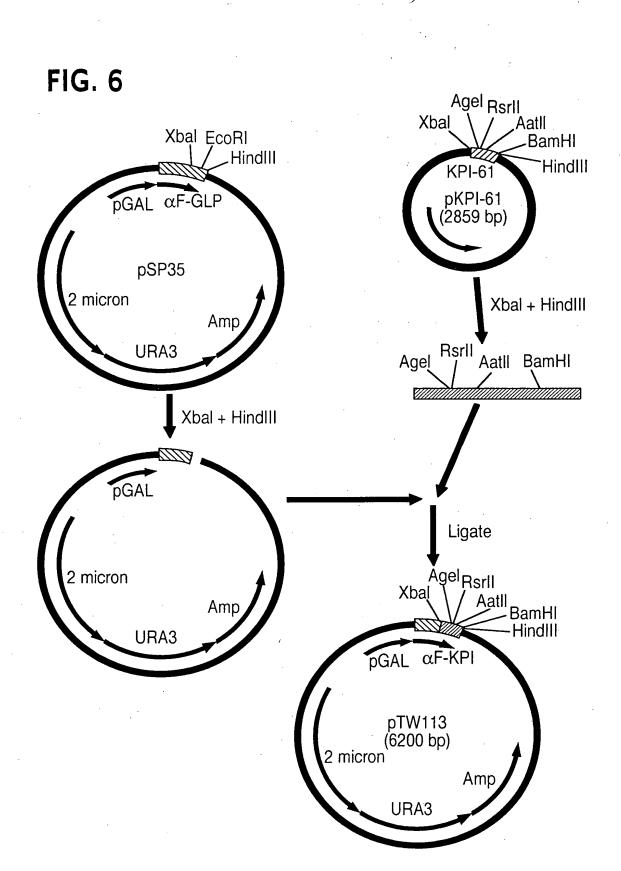
Hindll TA ATT (

ATT TAA 11e TCC GGA



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604





Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 7

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG ALA Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

• Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lie Asn Thr Thr lie Ala Ser lie Ala Ala Lys

Xbal

KPI(-4-57)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA ATG ATC TCC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT TAC TAG AGG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Met Ile Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG

Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHl

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 8

KPI(-4-57)

Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala -4 -3 -2 -1 1 2 3 4 5 6 7

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met - Ile - Ser - Arg 8 9 10 11 12 13 14 15 16 17 18

Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala 19 20 21 22 23 24 25 26 27 28 29

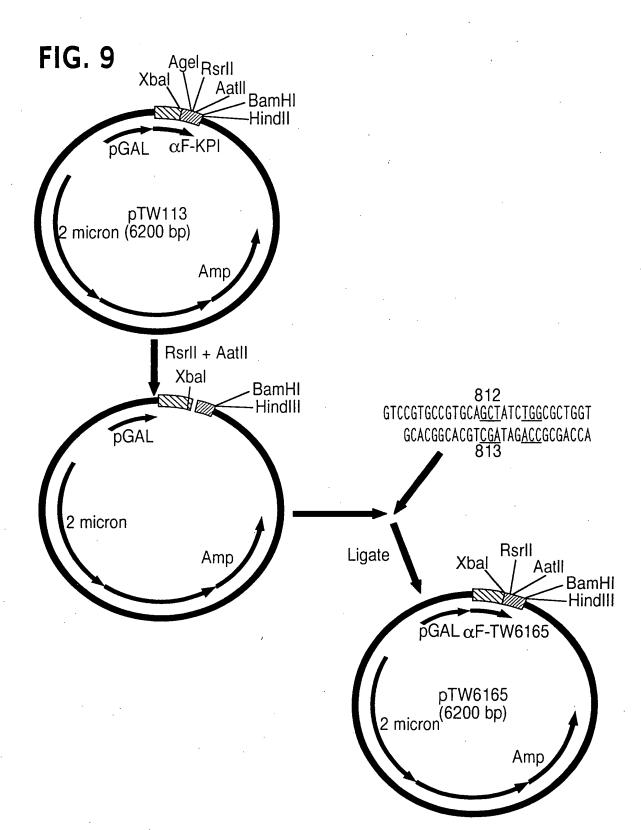
Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg 30 31 32 33 34 35 36 37 38 39 40

Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala 41 42 43 44 45 46 47 48 49 50 51

Val - Cys - Gly - Ser - Ala - Ile 52 53 54 55 56 57



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

pTW 6165

FIG. 10

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA ▶Met Arg Phe Pro Ser IIe Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln lle Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT ▶ Ser Thr Asn Asn Gly Leu Leu Phe lle Asn Thr Thr lle Ala Ser lle Ala Ala Lys

Xbal

KPI(-4-57; M15A, S17W)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT ▶Giu Giu Giy Val Ser Leu Asp Lys Arg Giu Val Val Arg Giu Val Cys Ser Giu Gin

Rsrll

Agel

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TGG CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT <u>CGA</u> TAG <u>ACC</u> GCG ACC ATG AAA CTG CAG TGA CTT ▶Ala Glu Thr Gly Pro Cys Arg Ala Ala lle Trp Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG-▶Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A ▶ Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 10/076,604

FIG. 11

812 FIG. 11	
GTCCGTGCCGTGCACCTATCTCCCCCCTGGTACTTTCACCGT CCACCGCACCG	pTW6165 KPI(-4-57; M15A, S17F)
814 GTCCGTCCCGTCCACCTATCTACCCCTCGTACTTTCACGT CCACCGCACCG	pTW6166 KPI(-4-57; M15A, S17Y)
867 GTCCGTCCCGTCCATTCCATCTTCCCCTCGTACTTTCACCGT CCACCGCACCG	pTW6175 KPI(-4-57; M15L, S17F)
1493 GTCCGTGCCGTCCA <u>TTG</u> ATC <u>TA</u> CCCCTCGTACTTTGACGT GCACCGCACCGT <u>AAC</u> TAG <u>ATG</u> CCCACCATGAAAC 1494	pBG028 KPI(-4-57; M15L, S17Y)
925 GTCCGTCCCGTCCAATC <u>CACTTCCCC</u> TCGTACTTCACGT CCACCGCACGTTAC <u>GTGAAC</u> ECCACCATCAAAC 926	pTW6183 KPI(-4-57; I16H, S17F)
927 GTCCGTCCCATCCACTACCCCTCGTACTTTCACGT CCACCGCACGTTAC <u>GTGATC</u> CCCACCATCAAAC 928	pTW6184 KPI(-4-57; I16H, S17Y)
929 GTCCGTGCCGTGCAATG <u>CACTGC</u> CCCTGGTACTTTGACGT GCACCGCACGTTAC <u>GTGACC</u> CCGCACCATGAAAC 930	pTW6185 KPI(-4-57; I16H, S17W)
863 GTOOGTOOGTOCA <u>OCTCAC</u> TOCOCCTOGTACTTTGAOGT CCACGOCACGT <u>OCAGTG</u> ACGGCGACCATGAAAC 864	pTW6173 KPI(-4-57; M15A, I16H)
865 GTOOGTGOOGTGCA <u>TTGCAC</u> TCOOGCTGGTACTTTGACGT GCACGGCACGT <u>AACGTG</u> AGGGCGACCATGAAAC 866	pTW6174 KPI(-4-57; M15L, I16H)



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 12

pTW 6166

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser IIe Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG ALA Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

• II e Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe IIe Asn Thr Thr IIe Ala Ser IIe Ala Ala Lys

Xbal

KPI(-4-57; M15A, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TAC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG ATG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Ala lle Tyr Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG GIy Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHl

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lie



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 13

pTW 6175

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG ALA Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln lie Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG lie Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lie Asn Thr Thr lie Ala Ser ile Ala Ala Lys

Xbal

KPI(-4-57; M15L, S17F)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT Giu Giu Giy Vai Ser Leu Asp Lys Arg Giu Vai Vai Arg Giu Vai Cys Ser Giu Gin

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA TTG ATC TTC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT AAC TAG AAG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Leu lle Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG

Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHl

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala ile



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

pBG028

FIG. 14

α -factor

ATG AGA TIT CCT TCA ATT TIT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG

Ala Pro Val Asn Thr Thr Glu Asp Glu Thr Ala Gln lle Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lle Asn Thr Thr lle Ala Ser lle Ala Ala Lys

Xbal

KPI(-4-57; M15L, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

RsrII

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA TTG ATC TAC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT AAC TAG ATG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Leu IIe Tyr Arg Trp Tyr Phe Asp Vai Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG GIy Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHl

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

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pTW6183

FIG. 15

α-factor

ATG AGA TIT CCT TCA ATT TIT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser IIe Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG

Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gin lie Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lle Asn Thr Thr lle Ala Ser lle Ala Ala Lys

KPI(-4-57; I16H, S17F)

Xbal

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU GIU GIU GIU Val Ser Leu Asp Lys Arg Giu Val Val Arg Giu Val Cys Ser Giu Gin

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA ATG <u>CAC</u> <u>TTC</u> CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT TAC <u>GTG AAG</u> GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Alá Met His Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG GIy Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

pTW6184

FIG. 16

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG

Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln lle Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG IIIe Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lie Asn Thr Thr lie Ala Ser lie Ala Ala Lys

Xbal

KPI(-4-57; I16H, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA ATG <u>CAC</u> <u>TAC</u> CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT TAC <u>GTG</u> ATG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Met His Tyr Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG

Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lie



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

pTW6185

FIG. 17

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA ▶ Met Arg Phe Pro Ser IIe Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG ▶ Ala Pro Val Asn Thr Thr Thr Giu Asp Glu Thr Ala Gin lle Pro Ala Giu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG ▶lle Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lle Asn Thr Thr lle Ala Ser lle Ala Ala Lys

Xbal

KPI(-4-57; I16H, S17W)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT ▶ Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA ATG <u>CAC</u> <u>TGG</u> CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT TAC GTG ACC GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Met His Trp Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A ▶Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

pTW6173

FIG. 18

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG ALA Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln lle Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe IIe Asn Thr Thr IIe Ala Ser IIe Ala Ala Lys

Xbal

KPI(-4-57; M15A, I16H)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU GIU GIU GIU Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gin

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA GCT CAC TCC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT CGA GTG AGG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Ala His Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG

Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

pTW6174

FIG. 19

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser IIe Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG ALA Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln lie Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lle Asn Thr Thr lle Ala Ser lle Ala Ala Lys

Xbal

KPI(-4-57; M15L, I16H)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GTU GIU GIU GIU GIU Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gin

RsrII

Agel

AatII

GCT GAG ACC GGT CCG TGC CGT GCA TTG CAC TCC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT AAC GTG AGG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Leu His Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG

Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHl

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 20

KPI(-4-57; M15A, S17W) TW6165



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 21

KPI(-4-57; M15A, S17Y) TW6166



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 22

KPI(-4-57; M15L, S17F) TW6175



Title: PROTEASE INHIBITOR

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FIG. 23

KPI(-4-57; M15L, S17Y) BG028



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 24

KPI(-4-57; I16H, S17F) TW6183



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 25

KPI(-4-57; I16H, S17Y) TW6184



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 26

KPI(-4-57; I16H, S17W) TW6185

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met -
$$\frac{His}{10}$$
 - $\frac{Trp}{10}$ - Arg 8 9 10 11 12 13 14 15 16 17 18



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 27

KPI(-4-57; M15A, S17F) DD185



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 28

KPI(-4-57; M15A, I16H) TW6173

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Title: PROTEASE INHIBITOR

PEPTIDES

Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

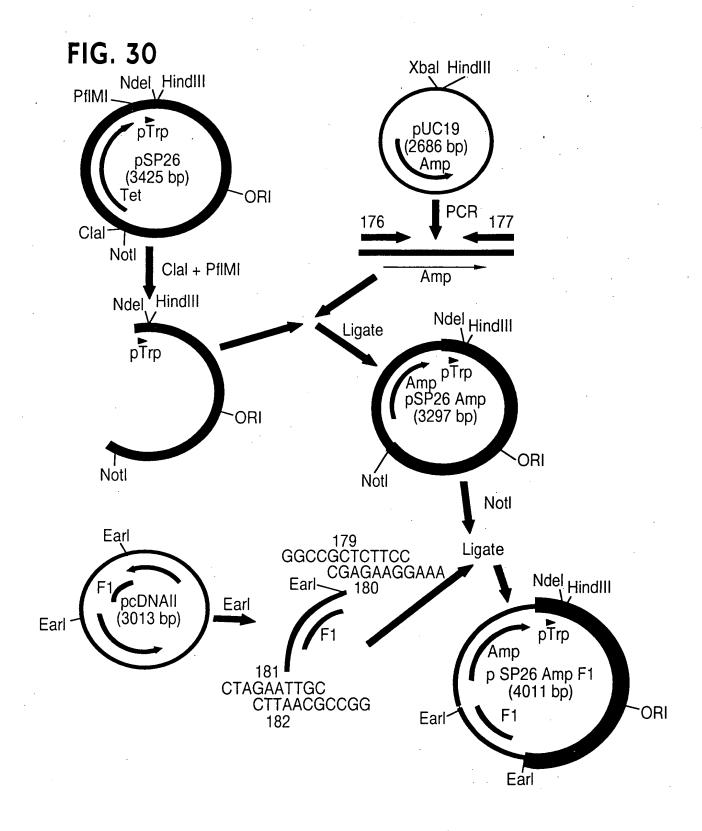
FIG. 29

KPI(-4-57; M15L, I16H) TW6174

Glu - Thr - Gly - Pro - Cys - Arg - Ala -
$$\underline{\text{Leu}}$$
 - $\underline{\text{His}}$ - Ser - Arg 8 9 10 11 12 13 14 15 16 17 18



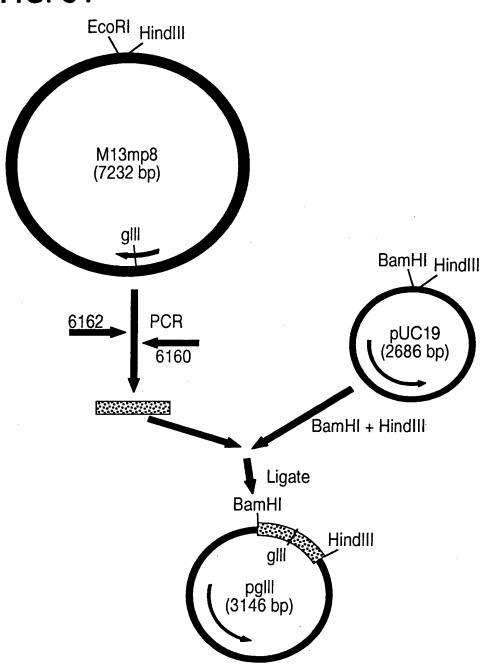
Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604





Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 31

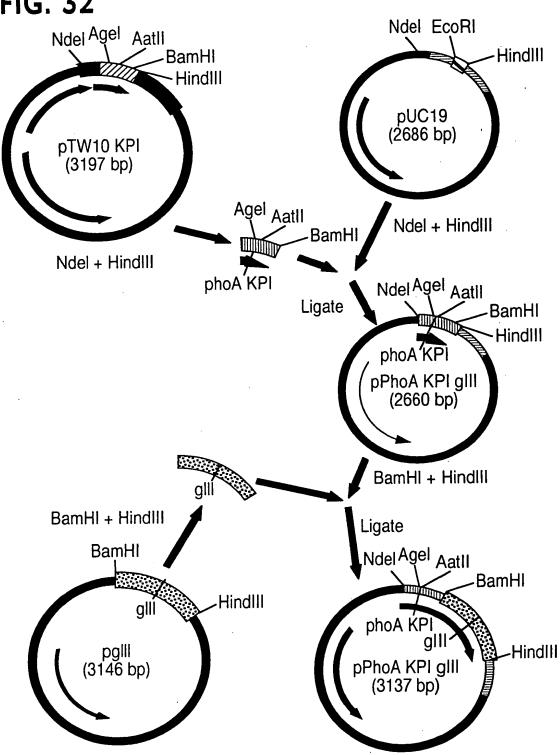




Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

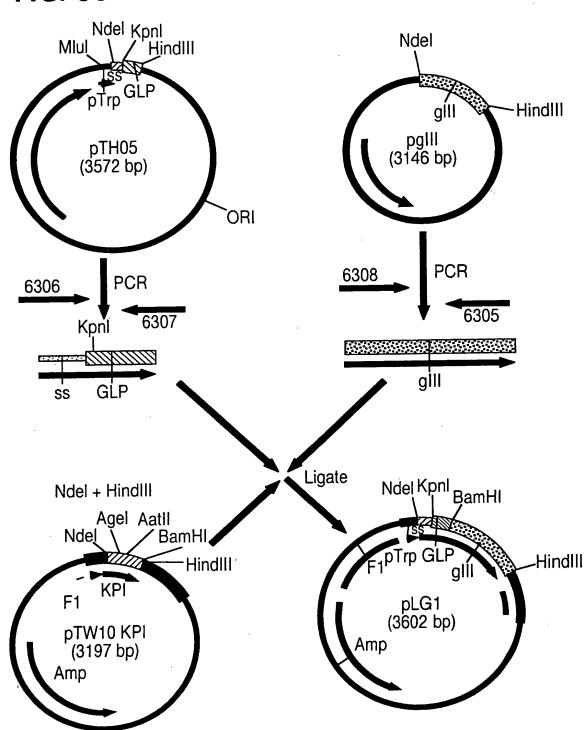
FIG. 32





Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

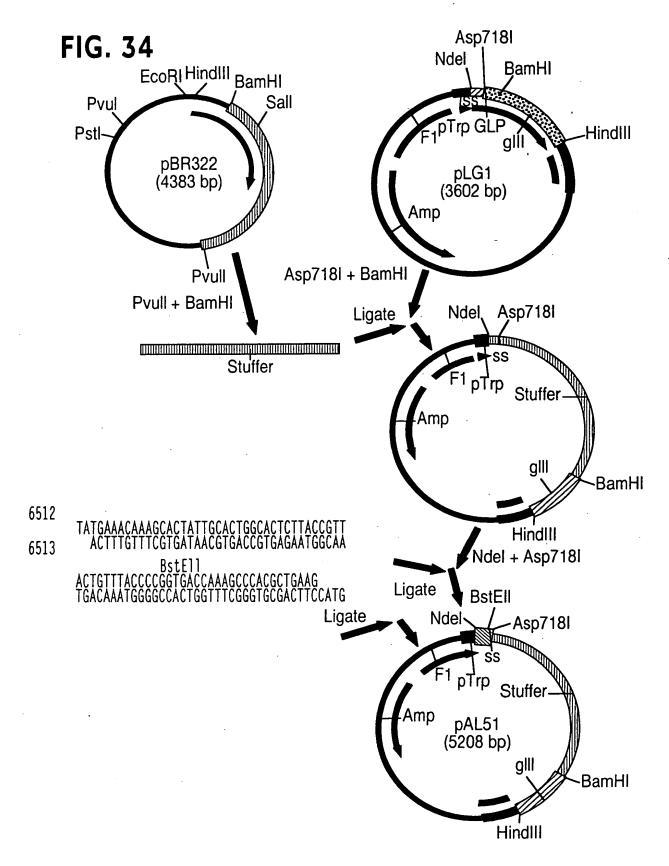
FIG. 33





Inventor(s): R. Tyler WHITE et al.

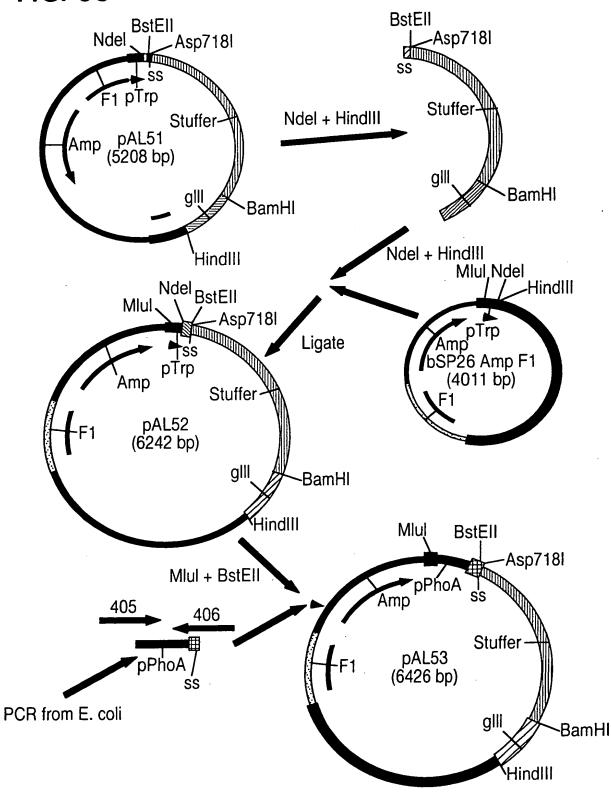
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Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

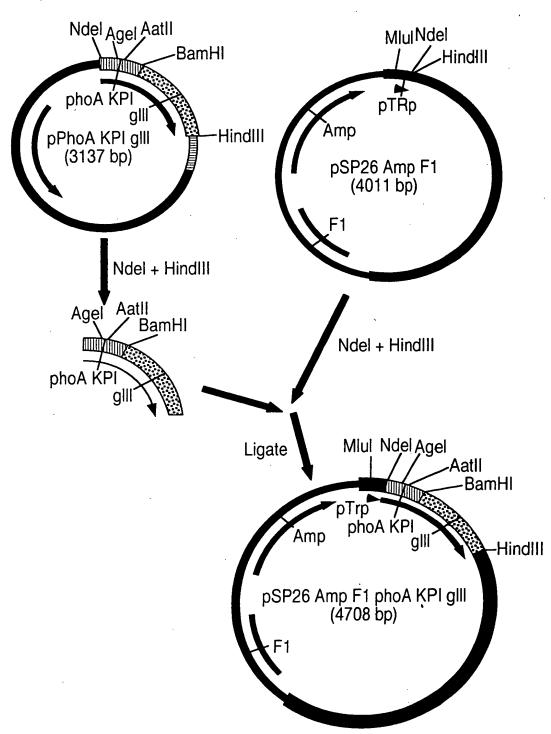
FIG. 35





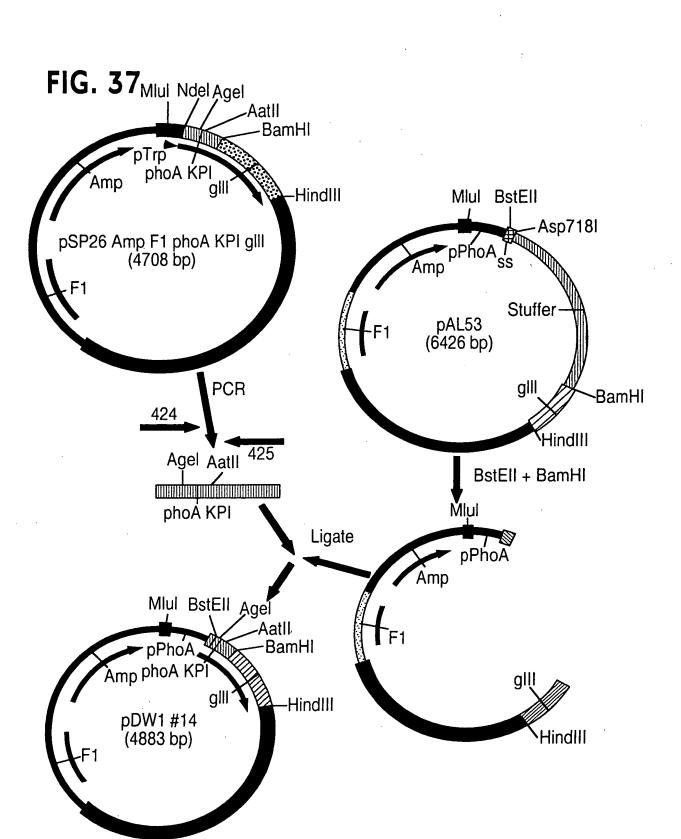
Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 36





Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604



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Title: PROTEASE INHIBITOR PEPTIDES

Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

phoA signal

FIG. 38

BstEll

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA Val Lys Gin Ser Thr lie Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI (1-55) Agel

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT GCA ATG ATC TCC CGC TGG

Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg Ala Met lle Ser Arg Trp

Aatll

TAC TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC

Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn

CGT AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGC TCT

Arg Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Gly Gly Gly Ser

GGT TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA big Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu

AAT GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT Asn Ala Asp Glu Asn Ala Leu Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr

GAT TAC GGT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT ASp Tyr Gly Ala Ala lie Asp Gly Phe lie Gly Asp Val Ser Gly Leu Ala Asn Gly Asn

GGT GCT ACT GGT GAT TTT GCT GGC TCT AAT TCC CAA ATG GCT CAA GTC GGT GAC GGT GAT IN GIV Ala Thr GIV Asp Phe Ala GIV Ser Asn Ser GIN Met Ala GIN Val GIV Asp GIV Asp

AAT TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA

ASn Ser Pro Leu Met Asn Asn Phe Arg Gin Tyr Leu Pro Ser Leu Pro Gin Ser Val Glu

TGT CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA VCs Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser Ile Asp Cys Asp Lys

ATA AAC TTA TTC CGT GGT GTC TTT GCG TTT CTT TTA TAT GTT GCC ACC TTT ATG TAT GTA

TTT TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA

Phe Ser Thr Phe Ala Asn IIe Leu Arg Asn Lys Glu Ser • • •



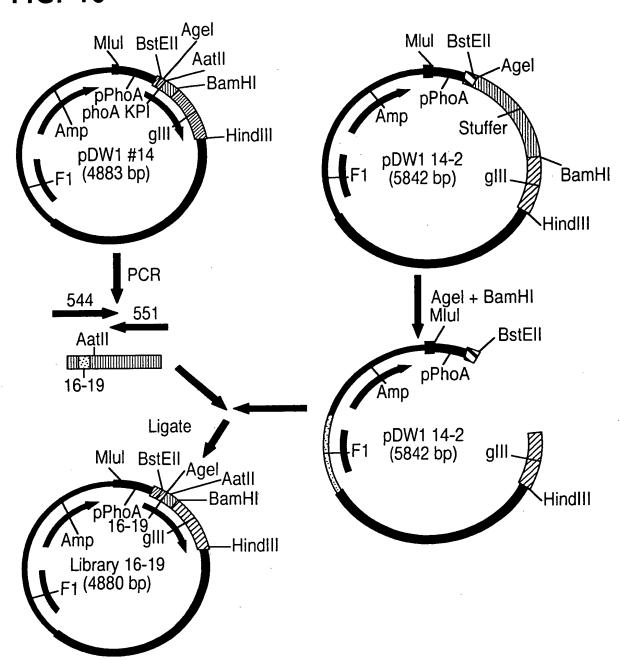
Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 39 Mlul BstEll Agel EcoRI HindIII BamHI Aatll Sall -BamHI Pvul pPhoA phoA KPI Pstl . Amp pBR322 HindIII pDW1 #14 (4363bp) 1 (4883 bp) **PCR** Agel + BamHl 266 Mļul BstEII 252 pPhoA Stuffer Amp **BstEll** glll HindIII Mlul Agel Ligate pPhoA -Stuffer Amp -BamHI pDW1 14-2 gIII (5642 bp) HindIII



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 40



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Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

phoA signal

FIG. 41

BstEII

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA

Val Lys Gln Ser Thr lie Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI (1-55; 16 - 19)

Agel

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT NNS NNS NNS NNS NNS TGG TAC

Ala Glu Val Cys Ser Glu Gin Ala Glu Thr Gly Pro Cys Arg --- --- Trp Tyr

Aatll

TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT

Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg

AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGC TCT GGT

Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Gly Gly Gly Ser Gly

TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA AAT Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu Asn

GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT GAT Ala Asp Glu Asn Ala Leu Gin Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr Asp

TAC GGT GCT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT GGT

Tyr Gly Ala Ala lie Asp Gly Phe lie Gly Asp Val Ser Gly Leu Ala Asn Gly Asn Gly

alli

GCT ACT GGT GAT TTT GCT GGC TCT AAT TĆC CAA ATG GCT CAA GTC GGT GAC GGT GAT AAT

Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln Val Gly Asp Gly Asp Asn

TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA TGT Ser Pro Leu Met Asn Asn Phe Arg Gin Tyr Leu Pro Ser Leu Pro Gin Ser Val Glu Cys

CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA ATA
Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser IIe Asp Cys Asp Lys IIe

AAC TTA TTC CGT GGT GTC TTT GCG TTT CTT TTA TAT GTT GCC ACC TTT ATG TAT GTA TTT AS AS Leu Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr Val Phe

TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA

Ser Thr Phe Ala Asn IIe Leu Arg Asn Lys Giu Ser • • •

Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

phoA signal

FIG. 42

BstEll

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA Val Lys Gin Ser Thr lie Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI (1-55; M15A, S17F)

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TTC CGC TGG Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg Ala Ala lle Phe Arg Trp

Aatll

TAC TIT GAC GIC ACT GAA GGT AAG TGC GCT CCA TIC TIT TAC GGC GGT TGC GGC GGC AAC Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn

BamHI CGT AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGT GGC TCT Arg Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Vai Cys Gly Ser Gly Gly Gly Ser

GGT TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA ▶Gly Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu

AAT GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT Asn Ala Asp Glu Asn Ala Leu Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr

GAT TAC GGT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT Asp Tyr Gly Ala Ala lle Asp Gly Phe lle Gly Asp Val Ser Gly Leu Ala Asn Gly Asn

GGT GCT ACT GGT GAT TTT GCT GGC TCT AAT TCC CAA ATG GCT CAA GTC GGT GAC GGT GAT Gly Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln Val Gly Asp Gly Asp

AAT TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA Asn Ser Pro Leu Met Asn Asn Phe Arg Gln Tyr Leu Pro Ser Leu Pro Gln Ser Val Glu

TGT CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA Cys Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser lle Asp Cys Asp Lys

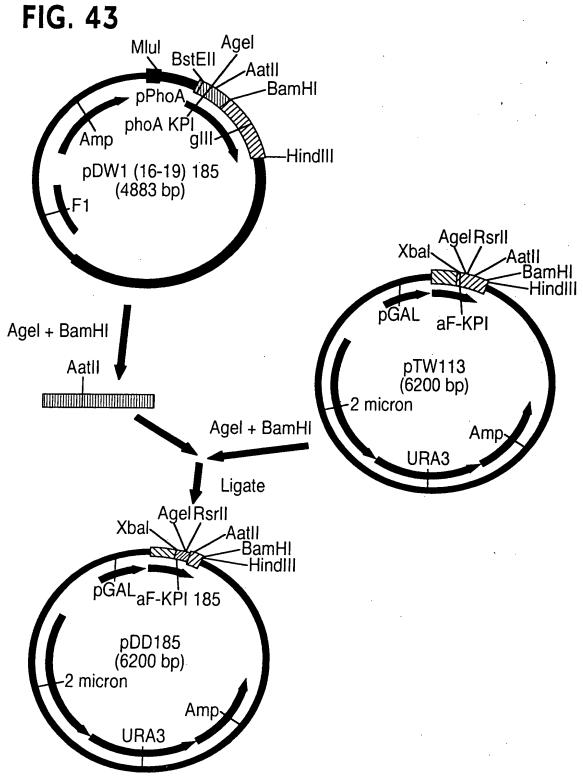
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TTT TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA ▶ Phe Ser Thr Phe Ala Asn lie Leu Arg Asn Lys Glu Ser



Title: PROTEASE INHIBITOR **PEPTIDES** Inventor(s): R. Tyler WHITE et al.

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Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

pDD185

FIG. 44

α -factor

ATG AGA TIT CCT TCA ATT TIT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG Ala Pro Val Asn Thr Thr Glu Asp Glu Thr Ala Gin lie Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG IIe Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lie Asn Thr Thr lie Ala Ser lie Ala Ala Lys

Xbal

KPI(-4-57; M15A, S17F)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gin

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TTC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG AAG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Ala lle Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG GIy Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHi

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 45

Plasma kallikrein inhibition by KPI (-4-57) variants

Variant			Substitution		K (nM)
		15	16	17	•
TW113	KPI (4-57)				45.00
DD185	KPI (4-57; M15A, S17F)	A		ഥ	0.39
TW6165	KPI (4-57; M15A, S17W)	A		≱	0.65
TW6166	KPI (4-57; M15A, S17Y)	A		> -	0.40
TW6175	KPI (4-57; M15L, S17F)	L		江	0.50
BG028	KPI (4-57; M15L, S17Y)	J		>	1.10
TW6183	KPI (4-57; 116H, S17F)		н	ഥ	1.20
TW6184	KPI (-4-57; 116H, S17Y)		Н	>	0.91
TW6185	KPI (4-57; 116H, S17W)		щ	≱	1.30
TW6173	KPI (4-57; M15A, 116H)	⋖	Н		1.00
TW6174	KPI (4-57; M15L, 116H)	'n	н		0.90



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 46A

			Inhibition Ki (nM)	Ki (nM)	
Variant	Sequence	kallikrci	Plasmin	XIIa	Σa
Aprotinin (RPDFCLEPPYTGPCKARI I RYFYNAKAGLOQTFVYGGCRAKRNNFKSARDCHRTCGGA	20.00	0.23	5000.0	
Aprotinin R15, S42	DFCLEPPYTGPCRARIIRYFYNAKAGLCQTFVYGGCRAKSNNFKSAEDCHRTCGGA	16:0	0.17	3983.0	
KPI (4-57)	EVVREVCSEQAETGPCRAMISRHYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	45.00	34.00	3718.0	161.0
TW6167	EVVREVCSEQAEPGPCRAMISRHYFDVTEGKCAPFFYGGCGGNRNNFDTEBYCMAVCGSAI	90:19		3641.0	288.0
BG031	EVVREVCSEQAEVGPCRAMISRMY PDVTEGKCAPP FYGGCGGNRNN PDTEBYCMAVCGSAI	34.00		498.0	
BG032	Evvrevcseqaesgpcramisrhyfdvtegkcapppyggcggnrnnfdteeychavcgsai	49.00		731.0	
TW101	EVCSEQAETGPCKAMISRWYFDVTEGKCAPPPYGGCGGNRNNFDTEEYCMAVCGSAI	2000.00	11.50		
TW6208	EVVREVCSEQAETGPCRGHISRWYPDVTEGKCAPPYGGCGGNRNNFDTEBYCMAVCGSAI			369.0	
TW106	EVCSEQAETGPCRARISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	260.00	3.70		
DD108	BVVREVCSEQAETGPCRAAISRMYFDVTEGKCAPFYGGCGGNRNNFDTEEYCMAVCGSAI	1.70	11.20	1600.0	123.0
DD109	BVVREVCSEQAETGPCRAIISRHYFDVTEGKCAPFFYGGCGGNRNNFDTEBYCMAVCGSAI	9.50		0.1891	421.0
DD110	EVVREVCSEQAETGPCRAL I SRMYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	2.10		624.0	\$5.0
11100	EVVREVCSEQAETGPCRAS I SRWYFDVTBGKCAPFYGGCGGNRNNFDTEBYCHAVCGSAI	5.60			
DD112	BVVREVCSEQAETGPCRAVISRWYFDVTEGKCAPPPYGGCGGNRNNFDTEBYCMAVCGSAI	08.9		0.866	
TW6179	BVVREVCSEQAETGPCRAGI SRHYPDVTEGKCAPPPYGGCGGNRNNFDTEBYCKAVCGSAI	78.00		368.0	



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PEPTIDES
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TW6163		\\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	33.		
	BY THE TOP WAS TO THE TOP THE SERVENT TOP TOP TOP TOP TOP TOP TOP TOP TOP TO	4.70	103.58	4532.0	457.0
TW6172	EVVRBVCSEQAETGPCRAMASRWYPDVTEGKCAPPYGGCGGNRNNFDTEEYCMAVCGSAI	315.00			1463 0
TW6180	EVVREVCSEQAETGPCRAMFSRWYFDVTEGKCAPFYGGCGGNRNNFDTERYCMAVCSSAI	70.00		8850	19.0
TW6181	EVVREVCSEQAETGPCRAMKSRWYFDVTEGKCAPFFYGGCGGRRNNFDTEEYCHAVCGSAI	150 00		15140	
BG001	EVVREVCSEQAETGPCRAMLSRWYFDVTBGKCAPPPYGGCGGNRNNFDTEEYCMAVCGSAI	38.00	89	0687	204.0
TW116	BVCSEQAETGPCRAMIIRWYPDVTEGRCAPPYGGCGGNRNNFDTBEYCMAVCGSAI	145.00	89.00		900
DD102	EVVREVCSEQAETGPCRAMIPRHYFDVTBGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	16.00		3150	
DD103	EVVREVCSEQAETGPCRAMIFRWYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	17.00		2128.0	991
DD104	EVVREVCSEQAETGPCRAMIYRWYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	15.00		237.0	1450
DD105	EVVREVCSEQAETGPCRAMIWRWYFDVTEGKCAPFFYGGCGGNRNNFDTEFYCHAVCGSAI	18.00		198.0	3000
TW6168	EVVREVCSEQAETGPCRAMILRHYPDVTEGRCAPFFYGGCGGNRNNFDTEEYCHAVGSAI	25.80		3810	3950
TW6182	EVVREVCSEQAETGPCRAMIHRMY FDVTEGKCAPFFYGGCGGNRNNFDTEFYCMAVCGSAI	36.00		75.0	
TW6194	EVVREVCSEQAETGPCRAMIERWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	20.83			
TW6210	BVVREVCSEQAETGPCRAMIQRHYPDVTEGRCAPPPYGGCGGNRNNPDTEBYCHAVCGSAI	8		2770	
9071D	EVVREVCSEQAETGPCRAMISAWYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCKAVCGSAI	110 20		0000	1330
BG012	EVVREVCSEQAETGPCRAMISTWYFDVTEGKCAPFFYGGCGGNRNNFDTEBYCHAVCGSAI			9	091
			-	-	



Title: PROTEASE INHIBITOR

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Appl. No.: 10/076,604

1 W0207	EVVREVCSEQAETGPCRAMI SHAY PDVTEGKCAPPFYGGCGGNRNNFDTERYCMAVCSSAT	00 18	06 57	184.0	613.0
TW6211	EVVREVCSEQAETGPCRAMISKWYPDVTBGKCAPPPYGGCGGNRNNPDTERYCMAVCSSAT	184 00	2	0.00	9.510
DD128	EVVREVCSEQAETGPCRAMISLWYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	4		0.40	37.0
TW6142	EVVRBVCSEQAETGPCRAMISRHYPDVTEGKCAPFVYGGCGGNRNNPDTEBYCKAVCGSAI	1800	18.00	7972.0	2250
AL301	EVVREVCSEGAETGPCRAMISRWYPDVTEGKCAPFLYGGCGGNRNNFDTERYCMAVCGSAI	216.00		15570	
AL302	EVVREVCSEQAETGPCRAHISRHYPDVTBGKCAPFGYGGCGGNRNNFDTBBYCHAVCGSAI	39.00			316.0
TW6147	EVVREVCSEQAETGPCRAMI SRHY PDVTEGKCAPPY GGCAGNRNN PDTEBY CHAVCGSAI	35.00		0.0601	179.0
TW6138	EVVREVCSEQAETGPCRAMISRHYFDVTBGKCAPFFYGGCKGNRNNFDTBEYCHAVCGSAI	18.00		921.0	309.0
TW6154	EVVREVCSEQAETGPCRAMISRHYPDVTEGKCAPFFYGGCLGNRNNFDTEBYCHAVCGSAI	11.00		915.0	39.0
TW6155	EVVREVCSEQAETGPCRAMISRHYPDVTEGKCAPFFYGGCHGNRNNFDTEEYCHAVCGSAI	8			27.0
TW6140	EVVREVCSEQAETGPCRAMISRHYPDVTEGKCAPPPYGGCNGNRNNPDTEBYCHAVCGSAI	35.00		4750	
TW6156	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCPGNRNNFDTEBYCMAVCGSAI				
TW6141	EVVREVCSEQAETGPCRAMISRWYPDVTEGKCAPFYGGCQGNRNNFDTEEYCHAVCGSAI	42.00			
TW118	EVCSEQAETGPCRAMISRWYPDVTEGKCAPPYGGCRGNRNNPDTERYCHAVCGSAI	89	24.00	13009 0	089
DDI00	EVVREVCSEQAETGPCRAHISRWYFDVTEGRCAPFYGGCCGNRNNFDTEBYCMAVCGSAI	15.00	<u> </u>		
TW6157	EVVREVCSEQAETGPCRAHISRWYFDVTEGRCAPFFYGGCSGNRNNFDTEBYCHAVCGSAI	80		8110	168.0
TW6158	EVVREVCSEQAETGPCRAMISRWYPDVTEGKCAPPYGGCTGNRNNPDTEEYCHAVGGSAI	29 00			



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FIG. 46D

TW6159	EVVREVCSEQAETGPCRAMISRHYPDVTEGKCAPPYGGCVGNRNNPDTERYCMAUCGSAT	17.00			0 77
TW6161	EVVREVCSEQAETGPCRAMISRHYFDVTEGKCAPPPYGGCYGNRNNFDTERYCMAVCGSAI	5	18.30	15070	2 2
DD101	EVVREVCSEQAETGPCRAMISRWYPDVTEGKCAPPYGGCDGNRNNPDTERYCMAVCGSAI	8		076	3
TW6151	EVVREVCSEQAETGPCRAMISRHYPDVTEGKCAPPFYGGCEGNRNNPDTEBYCMAVCGSAI	163.00		1162.0	9540
TW6139	EVVREVCSEQAETGPCRAHISRWYFDVTBGKCAPFFYGGCHGNRNNFDTEBYCMAVCGSAI	98	22.80	152.0	78.0
TW6153	EVVREVCSEQAETGPCRAMISRHYPDVTEGKCAPPFYGGCIGNRNNFDTEBYCMAVCGSAI	8:1	21.30	639	360
TW122	EVCSEQAETGPCRAMISRWYFDVTEGKCAPPFYGGCGANRNNFDTEBYCMAVCGSAI	32.00	27.00		0.185
TW6178	EVVREVCSEQAETGPCRAMISRHYPDVTEGRCAPPPYGGCGRNRNNPDTEBYCMAVCGBAI	90.91		4440	
TW6148	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPPYGGCGGARNNFDTEEYCHAVCGSAI	89			
TW124	EVCSEQAETGPCRAMISRWYPDVTEGKCAPPYGGOGGNSNNPDTEEYCHAVCGSAI	2	78.00		
TW6149	EVVREVCSEQAETGPCRAMISRWYPDVTEGKCAPPFYGGOGGNANNPDTEEYCMAVCGSAI	2 2	200		
TW6173	EVVREVCSEQAETGPCRAAHSRWYFDVTEGKCAPFFYGGOGGNRNNFDTEEYCMAVCGSAT	8	174	1430	
TW6174	EVVREVCSEQAETGPCRALHSRWYPDVTEGKCAPPYGGCGGNRNNPDTEEYCHAVCGSAI	8	08.9	286	
BG002	EVVREVCSEQAETGPCRALLSRWYPDVTEGRCAPPPYGGOGGNRNNPDTERYCMAVCGSAI	Š	200	0 20	U (V)
DD129	EVVREVCSEQAETGPCRALFSRWY FDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	360		18640	9
DD185	EVVREVCSEQAETGPCRAAIPRWYPDVTEGRCAPPFYGGCGGNRNNPDTEEYCMAVCGSAI	039	8.71	150.0	180



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TW6165	EVVREVCSEQAETGPCRAAIHRHY PDVTEGKCAPFFYGGCGGNRNN PDTEBYCHAVCGSAI	99'0	16.40	206.0	
TW6166	EVVREVCSEQAETGPCRAAIXRWYPDVTEGKCAPFYGGCGGNRNNFDTEEYCHAVCGSAI	0.4	10.10	73.0	
BG028	EVVREVCSEQAETGPCRALIYRHYPDVTEGKCAPPFYGGCGGNRNNFDTEEYCMAVCGSAI	1.10	12.10	93.8	
TW6169	EVVREVCSEQAETGPCRALILRHYPDVTEGKCAPPFYGGCGGNRNNPDTEEYCMAVCGSAI	1.20		0'619	111.0
DD113	EVVREVCSEQAETGPCRAL I PRWY PDVTEGKCAP FYGGCGGNRNN PDTEEYCMAVCGSAI	0.85	12.80	293.0	74.0
TW6175	Evvrevcsegaetgpcral i prhypdytegkcapppyggoggnrnpdteeychavcgsa i	05'0	7.46	35.0	\$6.0
TW6201	EVVREVCSEQAETGPCRAGIYRHYPDVTEGKCAPFFYGGCGGNRNNPDTEEYCHAVCGSAI	34.60		419.0	
TW6202	Evvrevcseqaetgpcragiwrhyfdvtegkcapppyggggggnrnpdteeychavcgsai	128.50		1237.0	
TW6203	EVVREVCSEQAETGPCRAGIPRHYPDVTEGKCAPPPYGGCGGNRNNPDTEBYCHAVCGSAI	31.20		5045.0	
TW6204	EVVREVCSEQAETGPCRAAISAHYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI		,	147.0	87.0
TW6205	EVVRBVCSEQAETGPCRAL I SAHY FDVTEGKCAPF FYGGCGGNRNNFDTBEYCHAVCGSAI			195.0	29.0
DD114	EVVREVCSEQAETGPCRAAISRWYFDVTEGKCAPFFYGGCRGNRNNFDTEEYCMAVCGSAI	0.70	1.11	224.0	
TW6190	EVVREVCSEQAETGPCRAAISRWYFDVTEGKCAPFFYGGCYGNRNNFDTEBYCMAVCGSAI	0.83	52.20	589.0	13%.0
TW6183	EVVREVCSEQAETGPCRAMHFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	1.20	11.68	12440.0	159.0
TW6184	EVVREVCSEQAETGPCRAMHYRWYPDVTEGKCAPPFYGGCGGNRNNPDTBEYCMAVCGSAI	16'0	11.96	14000.0	214.0
TW6185	EVVREVCSEQAETGPCRAHHRRY PDVTEGKCAPP YGGCGGNRNN PDTEEYCHAVCGSAI	1.30	18.60	388.0	473.0
BG003	EVVREVCSEQAETGPCRAMLHRWYPDVTEGKCAPFFYGGCGGNRNNPDTEBYCMAVCGSAI	36.00		467.0	



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FIG. 46F

TW6186	EVVREVCSEQAETGPCRAMHSRWYFDVTEGKCAPFFYGGCYGNRNNFDTBEYCMAVCGSAI	0.48	8.86	186.0	9
TW6187	EVVREVCSEGAETGPCRAMIFRWYFDVTEGRCAPFYGGCYGNRNNFDTERYCMAVCGSAI	3.80	15.40	92.0	15.0
TW6188	EVVRBVCSEQAETGPCRAMIYRWYFDVTEGRCAPFYGGCYGNRNNFDTBEYCHAVCGSAI	4.00		419.0	24.0
TW6189	EVVREVCSEQAETGPCRAMIWRWYFDVTEGKCAPPYGGCYGNRNNFDTEEYCMAVCGSAI	90.7			34.0
TW6170	EVVREVCSEQAEPGPCRALILRWY PDVTEGKCAPPYGGCGGNRNN PDTEBYCHAVCGSAI	2.50			452.0
DD115	EVVREVCSEQAETGPCRGY I TRWY PDVTEGKCAPPYGGCGGNRNN PDTEEYCHAVCGSAI			213.0	299.0
DD170	EVVREVCSEQAETGPCRALHNRWY PDVTEGKCAPPFYGGCGGNRNN PDTEBYCHAVCGSAI	0.99	18.00	550.0	
TW6176	EVVREVCSEQAETGPCRAAHPRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	3.50	118.00	56.0	
TW6177	EVVREVCSEQAETGPCRALHFRWYFDVTEGKCAPFFYGGOGGNRNNFDTBEYCHAVCGSAI	7.20	32.70	245.0	156.0
BG006	EVVREVCSEQAETGPCRAAL FRWY FDVTEGKCAP F F Y GGOGGNRNN F DTEEY CHAVCGSAI	0.30	12.10	80.0	
DD130	EVVREVCSEQAETGPCRALFTRWYPDVTEGKCAPPFYGGCGGNRNNFDTBEYCHAVCGSAI	5.50			9.5
DD131	EVVREVCSEQAETGPCRALFKRWYPDVTEGKCAPFYGGCGGNRNNFDTERYCHAVCGSAI	7.90	2.00	1385.0	3.3
DD132	EVVREVCSEQAETGPCRAPPKRHYPDVTEGKCAPPYGGCGGNRNNFDTEEYCHAVCGSAI	112.00			16.8
DD120	BVVREVCSEQAETGPCRAAFSAHYPDVTEGKCAPFYGGCGGNRNNFDTEEYCHAVCGSAI	8.30			0.11
DD121	EVVREVCSEQAETGPCRALLSAHY PDVTEGKCAP P PYGGGGGNRNN PDTEEY CHAVGGSAI	19.00			21.0
BG014	EVVREVCSEQAETGPCRALIHHHYPDVTEGKCAPPYGGCGGNRNNPDTEEYCHAVCGSAI	9.20	18.70	18.0	



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DD122	BVVREVCSEQAETGPCRALIFAHYFDVTEGKCAPFFYGGOGGNRNNFDTEEYCHAVCGSAI	15.00			46.0
BG015	EVVREVCSEQAETGPCRALIYHWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	90.9	12.20	19.4	597.0
BG020	EVVREVCSEQAETGPCRAAIHKWYPDVTEGKCAPFYGGGGGNRNNFDTEEYCHAVGGSAI	1.70		0.90	
BG022	EVVREVCSEQAETGPCRAAIYHWYPDVTEGKCAPFFYGGCGGNRNNFDTEEHCMAVCGSAI	99.0	7.26	3	
BG023	Evvrevcsegaetgpcraliqhwypdvtegkcapppygggggnrnnfdteeychavgsai	23,00		262.0	
BG024	EVVREVCSEQAETGPCRALIYKWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	4.10	7.47	38.7	
BG027	BVVREVCSEQAETGPCRAAIQHWYPDVTEGKCAPPPYGGCGGNRNNFDTEEYCHAVCGSAI	5.80		144.0	
91100	Evvrevcsegaetgpcraaifrhypdvtegkcapppyggcrgnrnpdteeychavcsai	0.14		\$83.0	84.0
TW6191	Evvrevcsegaetgpcraaiprwypdytegkcapppyggcygnrnnpdterychavcsai	0.26		0.499	20.02
DD117	EVVREVCSEQAETGPCRALIPRHYFDVTEGRCAPFYGGCRGNRNNFDTEEYCMAVCGSAI	0.11		1034.0	99.0
BG029	EVVREVCSEQAEVGPCRALIYHWYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	3.20		7.9	
BG030	EVVREVCSEQAESGPCRALIYHWYPDVTEGKCAPPPYGGCGGNRNNPDTEEYCHAVCGSAI	99.4		197	
BG033	EVVREVCSEQAEVGPCRAAIYHMYFDVTEGRCAPPYGGOGGNRNNFDTEEHCMAVOGSAI	0.75		5.6	



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BG034	BVVRBVCSEQAESGPCRAAIYHWYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	0.47		18.5	
BG040	EVVREVCSEQAEIGPCRALIYHWYPDVTEGKCAPEFYGGCGGNRNNFDTEEYCHAVCGSAI	340		98	
BG016	EVVREVCSEQAETGPCRGAIQHWYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	00.091		178.0	
BG017	EVVREVCSEQAETGPCRGAIRHWYPDVTEGRCAPFYGGCGGNRNNFDTEEYCMAVCGSAI	180.00		200.0	
BG021	EVVREVCSEQAETGPCRGSIRHWYPDVTEGKCAPFYGGOGGNRNNFDTEEYCHAVOGSAI	340,00		2240	
BG025	BVVREVCSEQAETGPCRGLIYHWYFDVTEGKCAPFFYGGOGGNRNNFDTEEYCMAVCGSAI	00 59		162	
BG026	EVVREVCSEQAETGPCRGAIYHWYFDVTEGKCAPFYGGOGGNRNNFDTEEYCHAVOGSAI	2000		34.9	
DD118	EVVREVCSEQAETGPCRALHNRWYPDVTEGKCAPFFYGGCRGNRNNFDTEEYCHAVCGSAI	0.53			
DD134	EVVREVCSEQAETGPCRALFKRHYPDVTEGKCAPFFYGGCYGNRNNPDTEEYCHAVGGSAI	0 1	<u> </u>	1.05 15640.0	90
DD135	EVVREVCSEQAETGPCRALFKRMYFDVTEGKCAPFFYGGCLGNRNNFDTEEYCMAVCGSAI	130		7473.0	60
DD136	EVVREVCSEQAETGPCRALFKRHY PDVTEGKCAPFFYGGCHGNRNN PDTEEYCHAVCGSAI	2			1.8



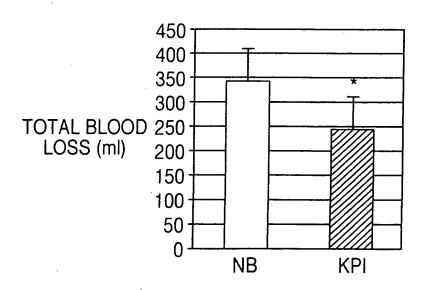
Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 47

VOLUMES

NS		344.25
KPI		245.75
	KDI	

KPI [245.75	
_	KPI	NS
	298	366
	266	342
	354	294
	258	385
	168	288
	266	469
	172	338
_	184	272
MEAN	245.75	344.25
STDEV	66.2414415	63.97488346
TTEST		0.009094999





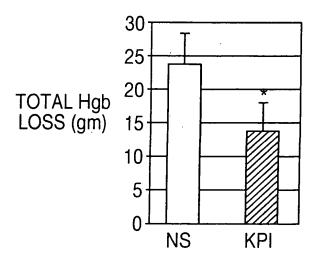
Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 48

HEMOGLOBIN

NS	23.61
KPI	13.59

KPI		<u> 13.59</u>	<u> </u>		
	KPI		NS		
		16.58		24.	95
		15.19)	24.	87
		20.21		20.	46
		8.99		27.	59
		14.63		18.	23
		15.31		31.	59
		7.7		23.	26
		10.14		17.	96
MEAN	13.	59375	23.6	613	75
STDEV	4.2	61438	4.0	687	<u>61</u>
TTEST			0.00	005	36





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FIG. 49

	Baseline PaO2	aO2	End CPB		Obs 60 min	.u	Obs 18
	KPI N	NS	KPI N	NS	KPI	NS	KPI
	652.2	620.9	495.7	60.5	483.7	441.3	
	654	559.2	444.6	132.2	330.1	448.7	792
	596.2	622.9	170.2	93.8	415.4	85.1	416
	606.2	689.2	264.2	333.9	430.2	529.6	36.
	633.1	665.1	567.2	341.7	613	568.3	<u>~</u>
	646.6	527	507.4	226.9	564.3	438.1	518
	563.2	461.7	547.1	89.1	501	42.6	49
	626.6	208	416.6	59.7	504.5	405.8	4
MEAN	626.425	288	426.625 167.225	167.225	480.275	480.275 369.938	37
STDEV	STDEV 34.4692 85.5055	5.5055	140.474 117.993	117.993	88.6187 196.523	196.523	150.27
	3	9	1	1	6	5	
TTEST	=d	0.268	<i>j</i> = <i>d</i>	0.0014	=d	p = 0.17915	

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Title: PROTEASE INHIBITOR **PEPTIDES**

Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

5.3

6.26

5.26 1.04

MEAN STDEV

13.59

245.75

MEAN STDEV

66.24

4.26

1.32

1.45 4.41

Dati	
of	ımes
ımarıy	Volun
Sum	Total

Serial Chest tube Hbg

120-180r	6.2	2.7	7.1	1.9	2.9	6.3	4.4	4.2
60-120min	9.8	6.7	2	4.4	7	5.6	5.4	5.4
30-60min	4.3	6.4	4.4	4	6.5	6.1	4.6	5.8
0-30min	3.7	4.3	4.1	2.8	6.3	4.1	3.1	6.9
Sacrifice	113	89	212	89	72	78	38	26
Chest tube	185	198	142	190	96	188	134	158
Total Hgb Loss	16.58	15.19	20.21	8.99	14.63	15.31	7.7	10.14
Total volume loss	298	266	354	258	168	266	172	184
	KPI-1	KPI-2	KPI-3	KPI-4	KPI-5	KPI-6	KPI-7	KPI-8

	_							- 1			ı
5.4	7.1	6.5	6.3	2.6	7.4	4.2	5.3		6.1	0.85	
6.1	9.7	7.5	7.1	5.2	7.3	5.8	9		6.58	0.91	
9.8	7.4	7.5	7.2	7.2	7	7.7	8.2		9.2	1.04	
7.7	7.2	5.4	8.4	7.5	4	7.5	7.4		68.9	1.44	
	ļ	·	· · ·					1	MEAN	STDEV	
92	106	42	82	148	208	120	99				
274	236	252	303	140	261	218	206				
24.95	24.87	20.46	27.59	18.23	31.59	23.26	17.96		23.61	4.69	
366	342	294	385	288	469	338	272		344.25	63.97	
NS-1A	NS-2	NS-3	NS-4	NS-5	9-SN	NS-7	NS-8		MEAN	STDEV	

NS

NS

 $p^* p = 0.004$ p = 0.002

 $p^* = 0.0005$

 $^*p = 0.009$